(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 03/002168 A1

(51) International Patent Classification[7]: A61L 31/04, 31/14, 31/16

(21) International Application Number: PCT/US02/20462

(22) International Filing Date: 28 June 2002 (28.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/302,245 29 June 2001 (29.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/002168 A1

(54) Title: POROUS SPONGE MATRIX MEDICAL DEVICES AND METHODS

(57) Abstract: Described are hemostasis devices useful for implantation in biopsy tracts, which devices comprise highly compact, dried hemostatic sponge elements. Preferred devices also include compacted sponge matrices exhibiting high density and rigidity in combination with high volumetric expandability when wetted. Also described are methods for making and using such devices.

POROUS SPONGE MATRIX MEDICAL DEVICES AND METHODS

BACKGROUND

The present invention relates generally to medical devices and methods. In one particular aspect, the invention relates to porous sponge matrix devices and materials which are medically useful, for example, to facilitate hemostasis when applied to or within patient tissues.

As further background, sponge matrix devices have found wide application in the medical (including veterinary) fields. Among other things, sponge matrices have been used to provide hemostasis, and to serve as substrates and/or scaffolds in the delivery of therapeutic chemicals, proteins, nucleic acids or cells to patients.

In one facet of medicine, tissue biopsies are often taken from suspect tissue for diagnostic purposes. A wide variety of core biopsy devices and methods have been proposed, all of which typically excise a volume of tissue from the patient. Such procedures can lead to internal bleeding within the biopsied tissues, both due to the removal of tissue and to the needle tract created to extend the sampling

portion of the device to the tissue site from which the biopsy is needed.

In current clinical practice, no measures are taken to try to stop or slow the internal bleeding, and the body is simply allowed to undertake its natural clotting and healing processes. This is perhaps due to the difficulties in treating the affected areas, which are often located in relatively deep tissue of the patient.

Needs exist generally in the medical field for devices, materials and methods for providing treatment of patient tissues, for example tissues from which biopsy samples have been obtained. Such devices, materials and methods, as utilized to treat biopsied tissues, would desirably minimize any further procedure or discomfort to the patient, and would be relatively simple to use. The present invention addresses these needs.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides medical devices that include a dry sponge matrix material in a compressed configuration. The preferred sponge matrix material of the invention defines pores and is stabilized in a compressed state, for example by drying the sponge matrix material in a compressed state. The preferred material is highly dense and compact when dry, but expands substantially when wetted. For example, in advantageous embodiments, the inventive compressed matrix material expands at least 100% by volume when wetted. The sponge matrix material desirably has a density, in its compacted, dry state, of at least about $0.05 g/cm^3$. The preferred matrix material is crosslinked, desirably with a polar crosslinking agent that imparts a hydrophilic character to the matrix material thus improving its wettability. Suitable crosslinking agents for these purposes include for instance polyepoxide compounds such as polyglycidyl ethers.

In preferred embodiments of the invention, the compacted or compressed sponge matrix material of the invention is incorporated in percutaneously-deliverable medical devices. Such devices are advantageously sized and configured for passage through needle and/or catheter cannulas. For example, the present invention provides a hemostasis device which comprise a compacted, dry sponge matrix, wherein the device is

sized for deployment through a cannula, for example a cannula of a diameter consistent with a core biopsy needle and/or associated catheter.

In another aspect, the invention provides a method for preparing an expandable sponge matrix, which comprises providing a hydrated or otherwise wetted, porous sponge matrix, and drying the material under compression. Drying can be conducted, for instance, by freeze drying or vacuum drying the sponge matrix. Compression forces may be applied in one dimension or multiple dimensions during the drying process.

The invention also provides a method for treating a patient which comprises implanting in the patient a medical device including a compressed sponge matrix of the invention as described above. In a preferred mode, this method provides hemostasis in a biopsy site from which a biopsy tissue sample has been taken.

The invention also provides a tissue biopsy method that includes inserting a cannula (such as a needle cannula) to extend to a tissue site for biopsy, the cannula having an associated cutting member for cutting a sample of tissue from the tissue site. The cutting member is used to cut the sample of tissue, which is extracted from the patient through the cannula. The method also includes delivering to the tissue site through the cannula a hemostatic element formed from a

dry sponge matrix stabilized in a compressed configuration and expansible when wetted.

The present invention provides improved medical devices including sponge matrices which can be used for example in providing hemostasis, and methods for preparing and using the matrices and devices. Additional objects, features and advantages of the invention will be apparent from the descriptions herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 provides a perspective view of a hemostatic sponge pellet device of the invention.

Figures 2A-2C provide cross-sectional views of various stages during the implantation of a compressed sponge pellet device of the invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

For the purpose of promoting an understanding of the principles of the invention, reference will now be made to certain preferred embodiments thereof and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations, further modifications and applications of the principles of the invention as described herein being contemplated as would normally occur to one skilled in the art to which the invention relates.

As disclosed above, the present invention provides medical sponge matrices which are useful *inter alia* in hemostasis implant devices. Preferred such devices include compact, dry, sponge elements configured for deployment through a cannula to a biopsy site. The invention also provides methods for using such devices and matrices in the treatment of patients, for example for treatment of biopsied sites. Further, the invention provides methods for preparing highly compact and dense sponge matrices which involve compressing sponge matrices while hydrated, and drying the matrices in their compressed state.

Sponge matrices in accordance with the invention will generally comprise porous, three-dimensionally stable bodies formed from suitable biocompatible matrix materials. For example, suitable biocompatible matrix

materials include naturally-occurring polymers and/or synthetic polymers. More preferred sponge compositions of the invention will comprise collagen as a matrix-forming material, either alone or in combination with one or more other matrix forming materials. In general, sponge matrices of the invention can be formed by providing a liquid solution or suspension of a matrix-forming material, and causing the material to form a porous three-dimensionally stable structure. Other methods are known and can be used within the scope of the present invention.

Illustratively, in the formation of a collagen sponge, a collagen solution can be prepared. The collagen may be derived from mammalian or other animal sources, for example, bovine, porcine or human sources. Synthetically-derived collagen may also be used. The determination of suitable collagen concentrations in the solution will be within the purview of those skilled in the art, with concentration ranges of about 0.05 g/ml to about 0.2 g/ml being typical.

Digestion of the collagen to form the collagen solution is usually carried out under acidic conditions, starting with ground, minced or otherwise comminuted collagen-containing tissue. Optionally, enzymatic digestion may be utilized using known enzymes for this purpose such as pepsin, trypsin, and/or papain. After digestion, the enzymes can be removed by suitable, known techniques.

In further preparative steps, the collagen solution is treated with a precipitating buffer solution to neutralize the pH and precipitate the collagen. This precipitation can occur during incubation over several hours or days. The resulting product can be dried directly, but is preferably crosslinked with a suitable crosslinking agent and then dried. Illustrative crosslinking agents for these purposes include glutaraldehyde, formaldehyde, carbodiimides, UV irradiation, or other crosslinking agents. In preferred embodiments of the invention, the crosslinking agent will contain polar groups that impart a hydrophilic character to the final sponge matrix material. Desirably, a polyepoxide crosslinker is utilized for this purpose, especially a polyglycidyl ether compound. Suitable such compounds include ethylene glycol diglycidyl ether, available under the trade name Denacol EX810 from Nagese Chemical Co., Osaka, Japan, and glycerol polyglycidyl ether available under the trade name Denacol EX313 also from Nagese Chemical Co. Typically, polyglycidyl ethers or other polyepoxide compounds utilized in the invention will have from 2 to about 10 epoxide groups per molecule. The use of such epoxides and/or other crosslinking agents which impart polar groups and a hydrophilic character to the resulting matrix will provide for good wettability and rapid hydration and expansion of hemostasis devices of the invention.

Preferred sources of collagen for use in the sponge matrices of the invention include extracellular matrix materials such as collagenous submucosal tissues, and other collagenous basement membrane materials. These include, for example, small intestinal submucosa, stomach submucosa, urinary bladder submucosa, liver basement membrane, and other basement membrane materials. For additional information as to these collagenous matrix materials and their preparation, reference can be made for example to U.S. Patent Nos. 4,511,653, 4,902,508, 4,956,178, 5,554,389, and 6,099,567, and International Publication Nos. WO9825637 and WO9822158, each of which is hereby incorporated herein by reference in its entirety. In forming sponge matrices of the invention, these materials are preferably processed and utilized under conditions which retain their favorable growth properties. This may include, for example, processing under conditions in which native proteins and/or other materials, for instance biotropic agents, are retained in their bioactive form. For example, the collagen sources, and resulting sponge matrices, may include active native substances such as one or more growth factors, e.g. basic fibroblast growth factor (FGF-2); transforming growth factor beta (TGFss); epidermal growth factor (EFG); platelet derived growth factor (PDGF); and/or other substances such as glycosaminoglycans (GAGs); and/or fibronectin (FN).

With reference to Fig. 1, in one embodiment of the invention, compact sponge matrices of the invention will be used in forming percutaneously-implantable medical devices. For example, the matrices may be used to provide a small sponge element such as a pellet 10 that is useful for implantation into biopsied tissues to facilitate hemostasis and/or to deliver agents. For deployment, sponge element 10 of the invention will be highly compacted and configured for passage through the cannula of a needle and/or a catheter such as that used to obtain core biopsies. Preferred sponge pellets of the invention will have compacted sizes having diameters "d" preferably less than about 2 millimeters so as to be deployable through a needle of corresponding size, e.g. a needle of size 6 French or smaller. Illustrative lengths "l" for sponge pellets of this diameter are less than about 3 centimeters, typically in the range of about 0.25 to about 3 centimeters. These diameters and lengths may of course be varied to suit a particular patient need.

Preferred dry, compressed sponge matrices (and devices formed therefrom) will be highly dense, typically having densities of at least about $0.05g/cm^3$, preferably in the range of about $0.05g/cm^3$ to about $0.2g/cm^3$, and more preferably about $0.075g/cm^3$ to about $0.2g/cm^3$. The preferred compacted sponge matrix will have sufficient rigidity to be deployed by passage through needles or catheters as discussed above, for

example by utilizing a pusher rod or other pusher element to force the sponge matrix device through the needle and/or catheter cannula. Expanded sponge densities (dry) will generally be less than the corresponding compacted densities. Typical expanded densities (dry) will range from about 0.01g/cm^3 to about 0.1g/cm^3, more preferably about 0.02g/cm^3 to about 0.07g/cm^3.

Sponge matrix materials of the invention will advantageously be highly expandable when wetted, so as to achieve an expanded configuration (see 10A, Fig. 1). Preferred sponge materials will exhibit the capacity to expand at least 100% by volume, more preferably at least about 200% by volume, and typically in the range of about 300% by volume to about 1000% by volume, when wetted to saturation with deionized water. Preferred sponge materials of the invention will also exhibit advantageous rates of expansion, achieving volume expansions as noted above in less than about 10 seconds, more preferably less than about 5 seconds, when immersed in deionized water.

The expanded sizes typical for hemostatic sponge pellets of the invention include diameters "D" of about 0.5cm to about 3cm, and lengths "L" of about 0.5cm to 3cm. Such levels of expansion and final sizes are expected to exert compression on surrounding tissues when implanted, so as to benefit the patient by

providing a hemostatic effect within the biopsied tissue. Alternatively or in addition, the pellets may deliver active agents to the implantation site and surrounding tissue.

Highly compact, dense sponge matrices of the invention can be prepared by first hydrating or otherwise wetting a porous sponge matrix, and then compressing and drying the element. Such preparative processes generally provide a more dense, rigid and stably compressed sponge matrix than processes such as simple compaction of the dry sponge matrix. Drying will be conducted sufficiently to stabilize the sponge matrix. For example, preferred drying procedures will reduce the liquid (e.g. water) content of the matrix to less than about 20% by weight, more preferably less than about 10% by weight. Compression forces will be applied so as to achieve a final density and/or configuration desired, and can be applied in one, two or three dimensions, including radially. For example, a sponge pellet prepared from the inventive matrices can have a generally cylindrical shape having a circular or multi-sided (e.g. square or rectangular) cross section, and can have a diameter approximating that or smaller than that of the needle and/or catheter cannula through which it is to be passed. The drying of the compacted element can involve lyophilization (or freeze drying) or vacuum drying at ambient or elevated temperatures. When processed in this fashion, upon removal of the compaction force, the sponge matrix is

stabilized structurally and remains in its highly dense and compacted state until contacted with a liquid susceptible to absorption by the matrix, for example body fluids. The pores of the matrix are thereby stably retained at a volume substantially reduced from their maximum volume, but return to a partially or fully expanded state when the matrix material is wetted.

Sponge elements or other devices of the invention may be formed individually by compaction/drying of an appropriately sized sponge element, or they may be individually excised from a larger compacted/dried sponge matrix.

For medical use, the compacted or compressed sponge matrix device can be sterilized using any suitable means, including for example radiation. The device will be suitably packaged in sterile packaging for medical use, to form medical articles of the invention. In this regard, products of the invention may include biopsy kits containing at least one needle for obtaining a biopsy, and at least one sponge pellet of the invention. Suitable biopsy devices including needles include for example Quick-Core® biopsy needles or Twist-Core® biopsy needles available from Cook Diagnostic & Interventional Products.

In use in a biopsy procedure, after a core biopsy has been obtained, sponge elements of the invention are

implanted into the biopsy site, for instance including the site of the excised tissue and/or the needle tract from the biopsy procedure. Implantation of the sponge element can be achieved through a cannula disposed within the biopsy needle tract. With reference now to Figs. 2A-2C, in a preferred method, the biopsy procedure is performed with a biopsy device including an outer cannula 20 and an inner sampling needle (not shown). The inner sampling needle is used to obtain the biopsy tissue from the target patient tissue area 21 and withdrawn from the outer needle cannula, which is left in place. Thereafter, a sponge element 10 of the invention can be passed through the outer cannula (Fig. 2A), for example using a rod 22 or other device or mechanism to force the sponge element through the outer cannula and out an opening thereof (Fig. 2B). If desired, multiple sponge elements can be delivered to a single biopsy site. After placement of the sponge element or elements of the invention, the outer cannula can be withdrawn (Fig. 2C), leaving the sponge devices in place in the affected tissue.

Sponge elements or other devices of the invention may also contain one or more active agents therapeutic to the patient. For example, they may include proteins or other substances which promote clotting, for example Thrombin and/or Fibrinogen. Alternatively or in addition, sponge elements or other devices of the invention may include local anesthetics to be delivered to the affected (e.g. biopsied) tissue, and/or growth

factors to promote tissue growth and healing within the affected tissue. Illustratively, such active agents can be included in the liquid used to wet the sponge prior to compression.

Sponge elements of the invention may also contain agents which promote further retention of the compressed, high density form of the elements. These may include for example starch, cellulose, sugars such as dextrose, or glycerin. Such agents can optionally be included in the liquid (preferably aqueous) used to hydrate or otherwise wet the sponge prior to compaction and drying.

For the purpose of promoting the further understanding of the present invention and its advantages, the following specific examples are provided. It will be understood that these examples are illustrative and not limiting of the invention.

EXAMPLE 1

Fifty grams of SIS tissue, cut into two-centimeter length pieces, are added to 200 milliliters of a 0.1% pepsin in 0.5 M aqueous acetic acid solution. The resulting preparation is incubated at 37°C for about 48 hours with stirring. Optionally, any undigested material at that point may be removed by centrifugation at 12,000 RPM for 20 minutes at room temperature. The gelled preparation is dialyzed (molecular weight cutoff

of 3500) against several changes of phosphate buffered saline (pH 7.4) over 48 hours at 4°C. The gelled solution is then stored at 4°C until ready for use. The chilled SIS gel is spread into a mold of desired shape and submersed in a collagen crosslinking solution. The crosslinking solution contains 2%vol/vol diglycidyl ether plus 20%vol/vol ethanol solution at 4°C for 3-6 days. The resulting crosslinked SIS forms are removed from the crosslinking solution and frozen in a -80°C freezer. The frozen SIS forms are then lyophilized over a period of approximately 8 hours. The SIS forms are then soaked in several baths of high purity water, ringing residual water from the SIS sponge material between rinses.

EXAMPLE 2

An SIS sponge material in hydrated form, prepared as in Example 1, is placed between two ridged plates and compressed. The plates are clamped so that compression is maintained, and the clamped structure is lyophilized over a period of approximately 1-2 hours. The rigid plates are removed, leaving the SIS sponge material in a highly densed, compacted, flattened shape. This compacted material is highly absorbent and expandable, and can be used in a variety of medical applications. In one embodiment a sponge pellet configured for percutaneous insertion through the cannula of a catheter and/or needle is cut from the compacted SIS sponge matrix.

EXAMPLE 3

A crosslinked SIS sponge matrix, prepared as in Example 1, was swollen in a 0.9% USP saline for injection solution. This material was used alongside a sample of GELFOAM in testing to determine the coagulation time of untreated whole human blood in the presence of the materials. The average clotting time for both materials was 8 minutes, within the normal coagulation time for human blood.

While the invention has been detailed in the foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiment has been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected. Further, all publications cited herein are considered indicative of the skills possessed by those in the art, and all such publications are hereby incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. A medical device, comprising:

a dry sponge matrix defining pores, said sponge matrix stabilized in a compressed configuration and expansible when wetted.

2. The medical device of claim 1, wherein said sponge matrix is formed from matrix-forming material including collagen.

3. The medical device of claim 1, wherein said device is configured for percutaneous delivery.

4. The medical device of claim 2, wherein said device is configured for percutaneous delivery.

5. The medical device of claim 1, wherein said dry sponge matrix is expansible at least about 100% by volume when saturated with deionized water.

6. The medical device of claim 2, wherein said dry sponge matrix is expansible at least about 100% by volume when saturated with deionized water.

7. The medical device of claim 6, wherein said dry sponge matrix has a density of least about $0.05 g/cm^3$.

8. The medical device of claim 7, wherein said dry sponge matrix has a density in the range of about $0.05g/cm^3$ to about $0.2g/cm^3$.

9. The medical device of claim 8, wherein said dry sponge matrix has a density in the range of about $0.075g/cm^3$ to about $0.2g/cm^3$.

10. The medical device of claim 1, wherein said sponge matrix comprises at least one biotropic agent.

11. The medical device of claim 1, wherein said sponge matrix comprises collagen from an extracellular matrix.

12. The medical device of claim 11, wherein said sponge matrix comprises at least one active biotropic agent from said extracellular matrix.

13. The medical device of claim 11, wherein said extracellular matrix is submucosa or basement membrane.

14. The medical device of claim 12, wherein said extracellular matrix is submucosa or basement membrane.

15. The medical device of claim 2, wherein said sponge matrix is crosslinked.

16. The medical device of claim 15, wherein said sponge matrix is crosslinked with a chemical crosslinking agent providing polar groups in the matrix.

17. The medical device of claim 16, wherein said crosslinking agent is a polyepoxide compound.

18. The medical device of claim 17, wherein said polyexpoxide compound is a polyglycidyl ether compound.

19. The medical device of claim 18, wherein said polygylcidyl ether compound is a diglycidyl ether compound.

20. A method for preparing a compressed sponge matrix, comprising, comprising:

providing a wetted porous sponge matrix;

compressing said wetted sponge matrix; and

drying said sponge matrix to form a dry, compressed sponge matrix.

21. The method of claim 20, wherein said sponge matrix is formed from matrix-forming material including collagen.

22. The method of claim 20, wherein said dry sponge matrix is expansible at least about 100% by volume when saturated with deionized water.

23. The method of claim 21, wherein said dry sponge matrix is expansible at least about 100% by volume when saturated with deionized water.

24. The method of claim 23, wherein said dry, compressed sponge matrix has a density of least about $0.05g/cm^3$.

25. The method of claim 24, wherein said dry, compressed sponge matrix has a density in the range of about $0.05g/cm^3$ to about $0.2g/cm^3$.

26. The method of claim 25, wherein said sponge matrix comprises at least one active biotropic agent.

27. The method of claim 20, wherein said sponge matrix comprises collagen from an extracellular matrix.

28. The method of claim 27, wherein said sponge matrix comprises at least one active biotropic agent from said extracellular matrix.

29. The method of claim 28, wherein said extracellular matrix is submucosa or basement membrane.

30. The method of claim 20, wherein said sponge matrix is crosslinked.

31. The method of claim 30, wherein said sponge matrix is crosslinked with a chemical crosslinking agent providing polar groups in the matrix.

32. The method of claim 31, wherein said crosslinking agent is a polyepoxide compound.

33. The method of claim 32, wherein said polyexpoxide compound is a polyglycidyl ether compound.

34. A device useful for providing hemostasis in a tissue biopsy site, comprising:

an element formed from a dry sponge matrix and configured for percutaneous delivery to the biopsy site, said sponge matrix stabilized in a compressed configuration and expansible when wetted.

35. The device of claim 34, wherein said sponge matrix comprises collagen and is crosslinked.

36. The device of claim 35, wherein said sponge matrix is crosslinked with a chemical crosslinking agent providing polar groups in the matrix.

37. The device of claim 36, wherein the chemical crosslinking agent is a polyepoxide compound.

38. The device of claim 37, wherein the polyepoxide compound is a polyglycidyl ether compound.

39. The device of claim 35, wherein said dry sponge matrix has a density of at least about 0.05 g/cm^3 and is expansible at least 100% by volume when wetted.

40. A sponge device, comprising:

a dry, compressed sponge matrix defining pores, said sponge matrix having a density of at least about 0.05 g/cm^3 and expansible at least about 100% by volume when saturated with deionized water.

41. A method for providing hemostasis in a biopsy site from which a biopsy tissue sample has been taken, comprising implanting in the biopsy tract a hemostatic element formed from a dry sponge matrix stabilized in a compressed configuration and expansible when wetted.

42. The method of claim 41, wherein said implanting is conducted percutaneously.

43. The method of claim 42, wherein said percutaneously implanting comprises delivering said hemostatic element through a cannula used in obtaining the biopsy tissue sample.

44. A tissue biopsy method, comprising:

inserting a cannula to extend to a tissue site for biopsy, said cannula having an associated cutting member for cutting a sample of tissue from the tissue site;

cutting the sample of tissue with said cutting member;

extracting the sample of tissue through said cannula; and

delivering to the tissue site through the cannula a hemostatic element formed from a dry sponge matrix stabilized in a compressed configuration and expansible when wetted.

45. The method of claim 44, wherein said cannula comprises a needle cannula.

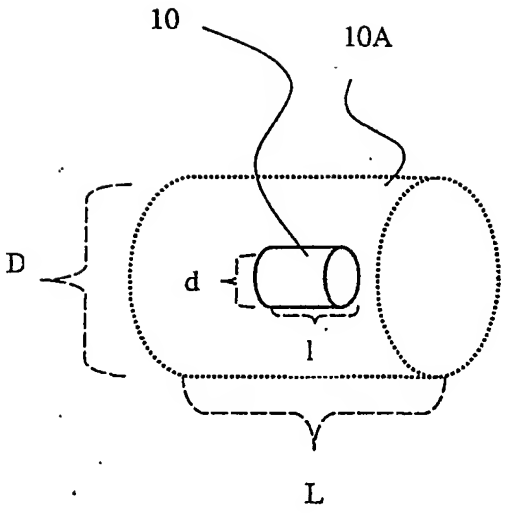

FIGURE 1

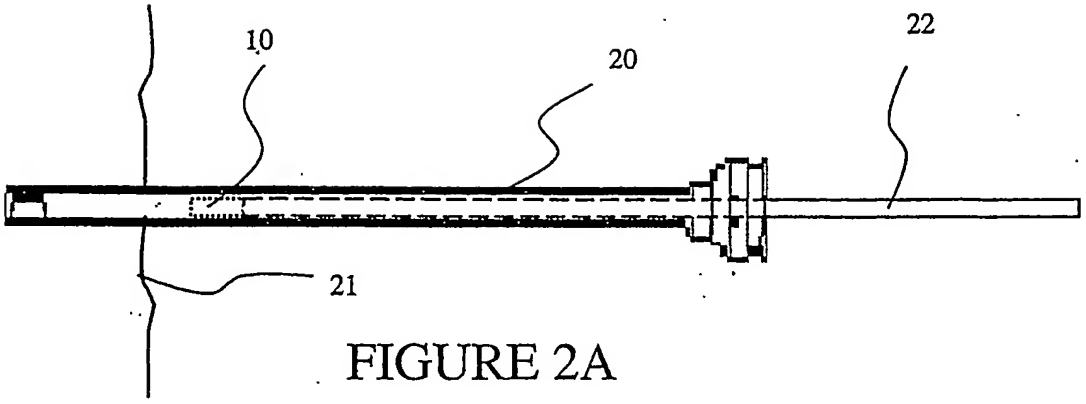

FIGURE 2A

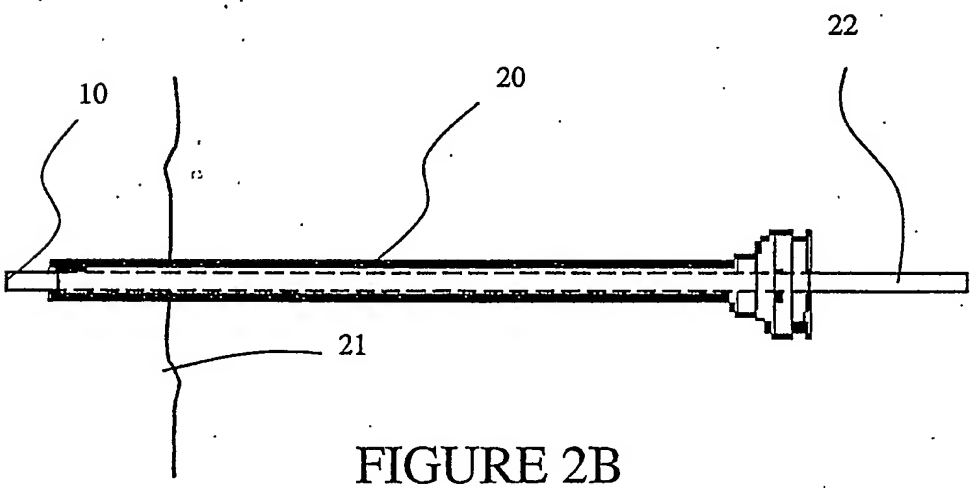

FIGURE 2B

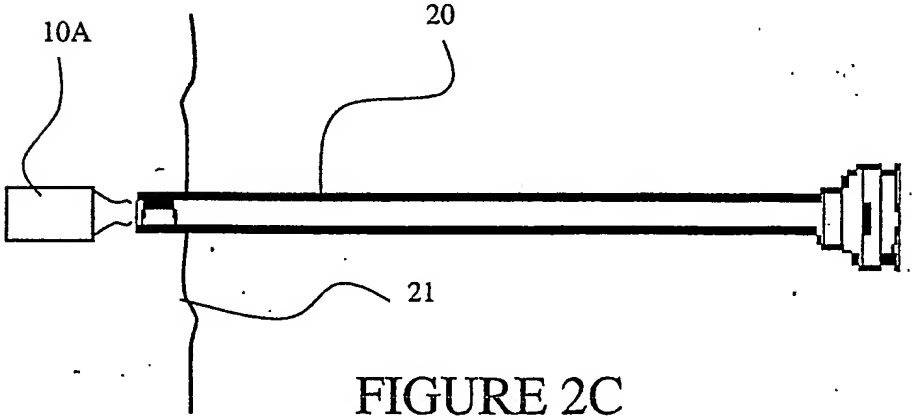

FIGURE 2C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/20462

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/04 A61L31/14 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 32250 A (PATEL UMESH H ;HILES MICHAEL C (US); COOK BIOTECH INC (US)) 8 June 2000 (2000-06-08)	1-15, 20-30, 34,35, 40-45
Y	page 2, line 1-9 page 4, line 8-12 page 11, line 15-28 page 12, line 3-14 page 13, line 26-29 page 14, line 17-23 examples 11,12	1-45
Y	EP 1 022 031 A (NISSHO KK) 26 July 2000 (2000-07-26) page 4, line 18-27 page 6, line 13-25	1-45

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2002	29/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhm, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	GB 887 844 A (JOHN STRAYTHORN ROBINS) 24 January 1962 (1962-01-24) page 3, line 40 -page 3, line 102	1
A	WO 01 13800 A (SUB Q INC ;ASHBY MARK (US); WHALEN VAUGHN P (US); CHI SING EDUARDO) 1 March 2001 (2001-03-01) page 3, line 15-19 page 6, line 3-10 page 19, line 10-19	1-6,10, 20,26,40
A	US 5 219 576 A (MCMULLIN HUGH ET AL) 15 June 1993 (1993-06-15) column 2, line 4-17 column 4, line 38-60 column 5, line 22-68 column 7, line 31-68	1-10,15, 20,26, 30,40

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 02/20462

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 41-45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the material (composition).

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/US 02/20462

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